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Letter to The Editor: "Vincristine Overdosage in Paediatric Patients"

I read with interest the review by Trinkle and Wu in May 1996 [1] concerning errors in the dosages of chemotherapy agents given to paediatric cancer patients. I wish to report a child who received a vincristine overdosage given over a few days rather than as a bolus dose.

The young boy had a rhabdomyosarcoma of the palate and was receiving radiotherapy and chemotherapy as part of his treatment protocol. During this phase he received daily vincristine for 6 days rather than weekly for 6 weeks. This resulted in a dose of $9mg/m^2$ (0,4mg/kg) given in 6 days.

During the first 2 doses of vincristine he had no complaints and a full blood count done on day 1 was normal including the white cell count and neutrophil count.

At the 3rd dose of vincristine he was complaining of sore throat and was pyrexial. He had clinical evidence of stomatitis that which thought to be due to the radiotherapy. He was put on antibiotics, paracetamol, and metronidazole. We used an oral rinse called Formulae C [2].

During the next 3 days he remained stable although ill. The temperature settled but a fine rash developed over the body and he was noted to be dull and apathetic. The stomatitis was more severe and his oral intake was decreased.

On the 8th day after the start of the vincristine he began to vomit and needed intravenous fluids to maintain his hydration. He began to spike a fever again and he was noted to be weak with decreased power and pain in the limbs. No stools had been passed since the first dose of vincristine.

On the 10th day after starting the vincristine he had 2 generalized convulsions and our error was realized. His convulsions were terminated with anticonvulsants and he was transferred to an intensive care unit. Electrolytes at this stage revealed a hyponatraemia and hypokalaemia. The white cell count was 0,44/ul but the haemoglobin and platelets were normal.

In the intensive care unit he was noted to be hypertensive and had evidence of a motor neuropathy with severe weakness and loss of power and reflexes in the limbs. He was treated conservatively with antihypertensives, anticonvulsants, and antibiotics. The neutropenia was treated with G-CSF and there was a marked rise in the neutrophil count over the next 5 days. The hyponatraemia and hypokalaemia were treated with 20% sodium chloride and 15% potassium chloride in appropriate doses.

On the 15th day after starting the vincristine the child was transferred back to the ward. At this stage his white cell count was normal, he was normotensive, apyrexial, and the serum electrolytes were normal. He was able to walk with support and had no signs of paralytic ileus. He continued to improve in the ward and eventually completed his radiotherapy and chemotherapy.

This boy illustrates all the described effects of a vincristine overdosage. He developed paralytic ileus, presumed SIADH, neutropenia, neurotoxicity (convulsions and motor neuropathy) as well as hypertension, vomiting, and a skin rash. The dose per kilogram he received is that described for both fatal and non-fatal cases [1] and perhaps the fact that the dose was spread over 6 days was a factor in improving our patients outcome.

This patient was treated symptomatically and supportively with antibiotics, fluids, and antihypertensives. We used Neupogen (G-CSF) to treat the neutropenia with very good results and the white cell count normalized within 5 days of starting the G-CSF.

This patient thus adds another to the list of patients who have received an overdosage of vincristine and survived using conservative treatment. It appears to be the first patient described in which Neupogen was used to treat the neutropenia.

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Letter to the Editor: "Spindle Cell (Kaposiform) Hemangioendothelioma With Kasabach-Merritt Syndrome in an Infant: Successful Treatment With α-2A Interferon (Deb et al., Med. Pediatr. Oncol. 28:358–361)"

In our case report on page 360, it is erroneously stated that we used ''Human interferon α-2a . . . as a sterile solution for subcutaneous injection . . . .'' It should have read: ''Human interferon α-2a . . . as the lyophilized powder (also containing sodium chloride and albumin), and reconstituted with normal saline . . . .''

We regret the error, and believe it is important to make the point that we have always used the desiccated, sterile powder rather than the dissolved product, which is formulated with alcohol. The ready-to-use solution has been implicated in the neurotoxicity seen in some infants with hemangiomas treated with interferon.

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Letter to the Editor: "Outcome of Post-Radiation Secondary Glioblastoma in Children"

Second primary brain tumor (SPBT) is defined by a histology different from the primary tumor and occurs after an interval of several years within the irradiation field [1]. The incidence of SPBT 10 years after radiation therapy (RT) alone is about 1% [2]. Low-dose cranial RT (i.e., 500 cGy) causes predominantly extra-axial tumors, while high-dose cranial RT (>1000 cGy) is more likely to cause malignant brain tumors [3]. A 2.3% incidence of SPBT (a 22-fold increase over the normal pediatric population) was found among 468 survivors of acute lymphoblastic leukemia (ALL) treated with chemotherapy and cranial RT [4]. Salvati et al. reviewed 88 cases of patients who presented with post-irradiation gliomas [5]: 32 of these had previous ALL, and this subgroup developed a malignant glioma in 70% of cases, with an interval of less than 10 years from the end of ALL therapy to the diagnosis of secondary glioma, in most cases.

Due to the rare occurrence of secondary gliomas, there are limited data on their evolution and response to therapy [6–8]. As more intensive treatments have recently been used in children with malignant brain tumors, we reviewed the outcome of aggressive multi-modality strategies in seven children with secondary glioblastoma (GBM).

The children in this study were referred for treatment of their brain tumor to Memorial Sloan-Kettering Cancer Center (MSKCC, NYC), Children's Hospital of Philadelphia (Philadelphia), and University of Nebraska Medical Center (Omaha). Histologic diagnosis of GBM was obtained in each case at surgery, and reviewed by the neuropathologist at MSKCC; two of these patients had also confirmation of progressive GBM at autopsy (cases 4 and 5). The age of patients at initial diagnosis of ALL or medulloblastoma (MB), the interval between cranial irradiation and presentation of the GBM, the treatment modalities, as well as time to recurrence and overall survival from diagnosis of GBM are shown in Table I.

The tolerance to additional intensive multi-modality therapy was good, but intensive multi-modality treatments for secondary GBM were unsuccessful in our patients. The median time to recurrence after diagnosis of GMB was 5 months (range 2–24 months), and the median overall survival was 10 months (range 6–24 months). These results are worse than those of children with primary GBM [9]. Taking into account its implied restrictions (i.e., repeated admissions to hospital, high cost, increased morbidity), intensive myeloablative chemotherapy does not seem currently appropriate for children with secondary glioblastoma.

Reports of treatment and evolution in secondary malignant gliomas are scarce. Tsang et al. in their discussion of four patients with glioma arising after RT for pituitary adenoma emphasize that the previous RT may have jeopardized the benefit from further effective irradiation [12]. This was reflected in our experience. Our longest surviving patient (24 months, case 2) had maximal resection of a cerebellar GBM; no RT was given after surgery, but the patient received intensive myeloablative chemotherapy. Iyer et al. reported a patient with astrocytoma arising after ALL who had a relapse-free survival longer than 19

TABLE I. Characteristics of Patients

Patient	Age at initial diagnosis[a]	Age at cranial RT/dose (cGy)	Age at GBM diagnosis/ location	Cranial RT-GMB interval (years)	Treatment of GBM[c]	Time to recurrence of GBM (months)	Overall survival after GBM diagnosis (months)
1	2/ALL	5/1,800	8 L. parietal	3	5,000 cGY Cx + BMR	6	13
2	4/ALL	5/2,400	8 Cerebellum	3	—[d] Cx + BMR	22	24
3	7/ALL	9.5/2,400	12 R. frontal	2.5	5,040 cGy Cx + BMR	10	12
4	5/ALL	5/2,400	18 L. parietal	13	3,600 cGy Cx + BMR	5	8
5	5/MB	5/3,600 n.a.[b] /5,600 p.f.	12 R. temporal	7	3,000 cGy Cx	2	9
6	5/MB	5/3,600 n.a.[b] /5,400 p.f.	13 Cerebellum	8	—[d] Cx + BMR	10	10
7	4/ALL	6/1,800 cranial 9/1,500 (TBI)	13 R. frontal	7	5,940 cGy	4	6
Median	5	5	12	7	—	5	10

[a]ALL, acute lymphoblastic leukemia; MB, medulloblastoma.
[b]n.a., neuraxis; p.f., posterior fossa.
[c]Conventional fractionated RT (total dose); Cx, chemotherapy (details upon request to authors); BMR; bone marrow rescue.
[d]Patient received no RT.

months, with surgery only [13]. These two anecdotal examples emphasize the role of surgery.

Identified risk factors that may affect the multi-step course of tumorigenesis, e.g., cranial RT for ALL, should be limited whenever possible [10]. The issue of causality in SPBT, whether induced by RT or only related to yet unknown genetic abnormalities underlying the ALL, is debated. Both increased incidence of leukemia in first-degree relatives of patients with brain tumors and brain tumors in relative of patients with leukemia have been reported, raising the possibility of a link between ALL and brain tumors [11].

Long-term follow-up with brain imaging is unlikely to be effective, given the rare occurrence of secondary gliomas. Most patients have rapidly occuring symptoms that command a diagnostic workup. The possibility of a neoplasm of different histology should be thoroughly investigated when a new mass lesion occurs after cranial RT for leukemia or primary brain tumor.

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Letter to the Editor: "Mesenchymal Chondrosarcoma of the Retroperitoneum"

Mesenchymal chondrosarcoma (MCS), first described by Lichtenstein and Bernstein in 1959, has been recognized as a rare tumor, with fewer than 200 documented cases [1,2]. It is characterized by areas of densely cellular and undifferentiated mesenchymal cells admixed with islands of mature hyline cartilage. The tumor can arise in soft tissue as well as bone, and extraskeletal MCS (EMCS) makes up 20–30% of the total [2,3]. Juvenile MCS originating from soft tissues in the retroperitoneum, as it did in our patient, has not been reported before.

He was a 9-year-old boy with complaints of a slowly growing lump in the right side of abdomen of 4 months duration without any pain or important past history. On physical examination, there was a non-tender, firm and fixed mass mainly in the right side of the abdomen, extending up to 20 cm below the right hypochondrial margin and well to the left side. Its left and lower margins could be defined, but the upper limit could not be palpated. He showed neither hepatosplenomegaly nor lymph node swelling. Laboratory examinations were negative including serum level of alphafetoprotein, neuron specific enolase, human chorionic gonadotropin and urinary levels of vanillyl mandelic acid and homovanillic acid. Abdominal computed tomography (CT) showed a retroperitoneal huge (16 cm) solid mass with speckled calcification, that occupied the right flank and pushed the kidney upward (Fig. 1). Chest X-ray films were negative. Exploratory laparotomy revealed a large, firm, fixed, and hypervascular retroperitoneal mass, occupying almost the whole of the right abdomen. The IVC and abdominal aorta were densely adherent to the tumor, making it unresectable. A wedge biopsy was therefore taken and the abdomen was closed. Microscopic examination showed findings consistent with EMCS. Postoperative arteriography showed a highly vascular tumor, fed mainly by the second and third lumbal arteries, through which 90 mg/m^2 of cisplatin (CDDP) and 60 mg/m^2 of doxorubicin (DOX) were injected. Systemic chemotherapy consisting of cyclophosphamide (CPM), vincristine (VCR) and etoposide was started. As there was no change in tumor size, embolization of the feeding arteries was followed by resection of the tumor together with the right kidney and IVC. The tumor, weighed 1,100 g, and measured 20 × 15 × 10 cm. Macroscopically, there was a mixture of yellow-red solid tissue with some cartilage, and microscopically, the tumor was composed of the two basic cellular components described in EMCS. The first was composed of undifferentiated round or spindle-shaped mesenchymal cells, possessing ovoid and elongated hyperchromatic nuclei and sparse irregular cytoplasm (Fig. 2). The second component was made up of small islets or nests of cartilaginous cells. The postop-

Fig. 1. CT shows a retroperitoneal huge solid mass with speckled calcification, maximum diameter 16 cm, occupying the right flank and pushing the kidney upward.

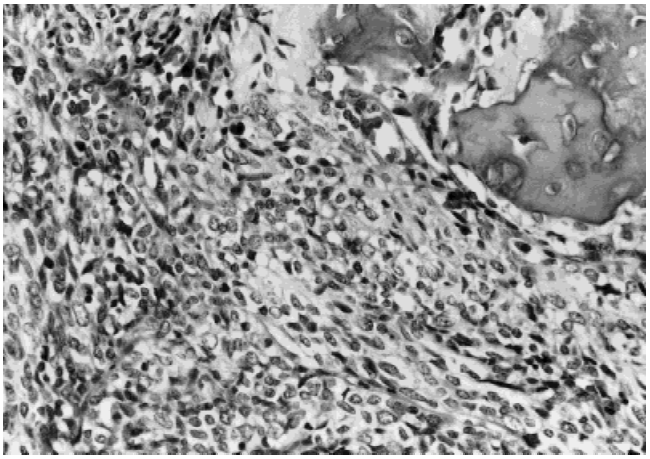

Fig. 2. Mesenchymal chondrosarcoma containing sheets of undifferentiated mesenchymal cells, well-differentiated cartilage, and osteoid. (HE ×100).

TABLE I. Clinical Features of Five Mesenchymal Chondrosarcomas of the Retroperitoneum

Case	Sex	Age	Size, cm	Treatment	Follow-up	Reference
1	M	61	20	Biopsy Irradiation Chemotherapy	2 yr, dead, recurrence, metastasis to lungs	Guccion [4]
2	M	30	–	Biopsy	no follow-up	Dhaliwal [7]
3	M	23	13	Resection	6 mo, dead, recurrence, metastasis to lungs complication	Doria [6]
4	F	27	20	Biopsy Chemotherapy	9 mo, dead, metastasis to lungs	Gonzalez-Campora [5]
5	M	9	20	Chemotherapy Resection	2 mo, dead, complication	present case

erative course was complicated by bleeding and duodenal perforation, and the boy died 75 days after tumor resection.

The histologic appearance of the tumor in our patient, and the lack of specific immunohistochemical markers are typical of this rare tumor. His age was unusual in that the tumor commonly occurs in the 2nd and 3rd decades of life with a predominance in females. The prognosis for MCS is poor. In a group of 23 patients from the Mayo Clinic, the 5-year survival rate was 54.6% and 10-year survival rate was 27.3% [2]. Forty three of 71 patients (60%) developed metastases, usually in the lung. There was no difference in survival in the groups with skeletal or soft tissue primary lesions, the latter being found most often in the orbit, cranial and spinal meningeal coverings, and lower limbs, particularly the thigh [2]. In rare instances, cases have been found in the mediastinum, hand musculature, retroperitoneum, brain, kidney or lung. To our knowledge, there have been only 4 prior cases of retroperitoneal MCS reported, all in adults [4–7]. Table 1 lists some of their clinical features, and includes our patient. It can be seen that the prognosis is poor. Radical surgery remains the mainstay of therapy. Multi-agent chemotherapy was not helpful in our experience.

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Letter to the Editor: "Diabetes Insipidus Associated With Langerhans Cell Histiocytosis: Is It Reversible? (Broadbent and Pritchard, Med. Pediatr. Oncol. 28:289–293)"

The article by Broadbent and Pritchard [1], who suggested that reported responses to treatment may in fact represent spontaneous regression of partial hormone deficiency in Langerhans cell histiocytosis (LCH)

prompted us to describe the course of partial diabetes insipidus. It was diagnosed by a water-deprivation test in a boy with biopsy proven LCH.

There was spontaneous regression concomitant with a decrease in the width of the previously thickened stalk on MRI.

The initial symptoms of polyuria and polydipsia had disappeared in this patient even before biopsy from the one single osteolytic defect in the frontal convexity was done. External irradiation was given only to the lytic defect. The pituitary received no irradiation and thus the changes mentioned above were accepted as spontaneous.

Dunger et al. [2] reported complete spontaneous recovery of posterior pituitary function in a patient with LCH. In our patient, repeat water-deprivation test, done after irradiation and in the absence of polyuria and polydipsia, has shown that the renal concentrating capacity was completely recovered but the posterior pituitary function, as indicated by a plasma arginine vasopressin (AVP) level, low in relation to urine osmolality [3], was still not normal. Nevertheless, our experience with this patient indicates, for the first time to our knowledge, that spontaneous recovery of urinary concentrating capacity during the course of LCH may be associated with a spontaneous improvement of MRI changes.

As we had not measured the plasma AVP level during the initial water-deprivation test, we do not know if the recovery of urinary concentrating capacity is a reflection of increased, albeit still low, AVP secretion. Although the concomitant improvement on the MRI suggests that this might be the case, the increased sensitivity of renal vasopressin receptors [4] might also be an explanation for the recovery of urinary concentrating capacity.

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Reply

Dr. Ercan et al.'s interesting case of spontaneous regression of diabetes insipidus in a patient with LCH illustrates the importance of thorough documentation of the disease both biochemically and by MR imaging.

Historic reports of diabetes insipidus responding to radiotherapy could equally have been spontaneous regression as many of these patients did not have biochemical or imaging studies. They were treated on clinical grounds when they developed thirst and polyuria.

In the series reported by Dunger [1] and in our series to which Dr. Ercan et al refer, the maximum urine osmolality after a short (7 hr) period of water deprivation together with measurement of urinary arginine vasopressin showed good discrimination between normal, partial, and non-function of the posterior pituitary. This test can be administered as an out-patient, it is completely non-invasive and is tolerated well.

A large prospective study of newly diagnosed LCH patients measuring these parameters at regular intervals together with gadolinium enhanced MR imaging would determine the incidence of partial DI (maximum urine osmolality 600–800 mosmol/kg; urinary AVP 30–90 pmol/l) and document its natural history. It would allow determination of the incidence of spontaneous regression and answer the question whether complete DI (maximum urine osmolality <300 mosmol/kg; urinary AVP <30 pmol/l) is ever reversible. Such a study has been proposed in the report of the Histiocyte Society's Workshop on CNS disease in LCH [2].

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Letter to the Editor: "Bone Pain Palliation With Strontium-89 in Children"

We read with interest the article by M. Charron et al. entitled ''Pain Palliation with Strontium-89 in Children with Metastatic Disease,'' published in *Medical and Pediatric Oncology* in June 1996 [1]. Strontium-89 (89 Sr), a beta emitting radioisotope with a specific uptake in bone, is generally employed for the palliation of metastatic bone pain in prostatic or breast cancers. The article reports the first cases of using 89 Sr in two children.

One patient had metastatic pulmonary carcinoma but only minimal increased uptake on bone scan. The authors recognize that the biodistribution of strontium is similar to 99mTc-MDP, thus, the failure of the treatment was predictable in that case.

The other patient was an 11-year-old boy with a stage IV neuroblastoma. Neuroblastoma is among the most common malignant neoplasms in childhood [2]. Since the early 1980s, the detection of neuroectodermally derived tumors has been greatly facilitated by the introduction of meta-iodobenzylguanidine (MIBG), an aralkylguanidine noradrenaline analogue [3,4]. Once iodinated with I-131 or I-123, mIBG has been shown to be highly sensitive (90–95%) and specific (100%) for the localisation of neuroblastoma lesions [5]. Furthermore, the great majority of authors claim that mIBG scintigraphy is more sensitive than bone scan for the detection of osseous and bone marrow involvements in neuroblastoma [6,7].

The high tumor affinity allows the therapeutic use of the 131I labelled mIBG [8]. The effectiveness of the treatment of neuroblastoma with 131I-mIBG is not only on bone pain palliation, like bone-seeking beta-emitting radionuclides such as 89 Sr, but encouraging results in term of partial or complete remission were reported in many clinical trials [9–12].

As mIBG is now widely available and commonly used, this exam, which reveals skeletal as well as soft tissue involvements, should be first performed in the diagnosis and follow-up of neuroblastoma. In the same manner, the potentiality of mIBG therapy in term of subjective as well as objective effects, should be better explored in neuroblastoma patients.

Therefore, even if the article [1] reports the first use of 89 Sr in children, the utility of the administration of that radioactive compound is questionable in both cases.

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Reply

We thank Drs. Giammarile and Chauvot for their interest in our paper, and for their review of the basics of nuclear medicine physics. We would like, however, to emphasize some features that were overlooked. From a radiation protection perspective iodine-131 is significantly more tedious to handle, and thus potentially more noxious than strontium-89; this is illustrated in the United States by stringent regulations that require patients who receive iodine-131 to be hospitalized when the dose of iodine-131 delivered is above 30 millicurie.

There are no such limitations or regulations with strontium-89 and thus patients can be released immediately. Side effects and complications of MIBG-I^{131} are also more severe; hematological toxicity continues to represent a limiting factor [1] especially in children with extensive bone marrow metastasis in whom bone marrow depression can be severe [2]. A recent study disclosed that MIBG-I^{131} had a sensitivity of only 50% for depiction of site of relapse [3]. Therefore one could predict that the therapeutic response would be even less in this group of patients. In terms of the efficacy of MIBG as a therapeutic agent, out of 95 patients reported in six different studies [4–9] only five had a complete response and 16 a partial response. In virtually all these patients bone marrow toxicity was observed and in some was manifested as severe thrombocytopenia (platelet level less than 25,000 per μL), and occasionally marked leukopenia was also present. A few patients developed renal and liver toxicity. Recently, a case report of hepatic necrosis was added to the list of complications [10]. Conversely, strontium-89 has been documented, in many prospective multi-center clinical trials, to be efficacious for pain palliation in adults with metastatic bone disease. The next logical step was thus to use this agent in children with metastatic disease to the bone. This was our goal and we intend to use it again in a prospective clinical trial in children with other neoplasia known to metastasize to the bone such as osteosarcoma, Ewing sarcoma and other tumors. We are puzzled that Drs. Giammarile and Chauvot question the utility of strontium-89 when we reported a successful outcome. Additionally, this child had lung cancer, and MIBG has no affinity for this neoplasm. In our opinion, it is counterproductive to be reluctant to accept a new treatment modality, regardless of what else is available. MIBG-I^{131} is not available for therapeutic use in the United States. The efficacy of MIBG-I^{131} is dubious and whether it will improve the prospect of cure remains to be seen [11]. Until MIBG-I^{131} is well accepted by the medical community, is readily available and is part of the armamentarium available to the physician, strontium-89 remains a better agent for palliation of pain in children and adults with metastatic bone disease.

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